In vitro/in vivo/in silico models to support bridging strategies from SC to SC, from IV to SC and vice versa

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Content

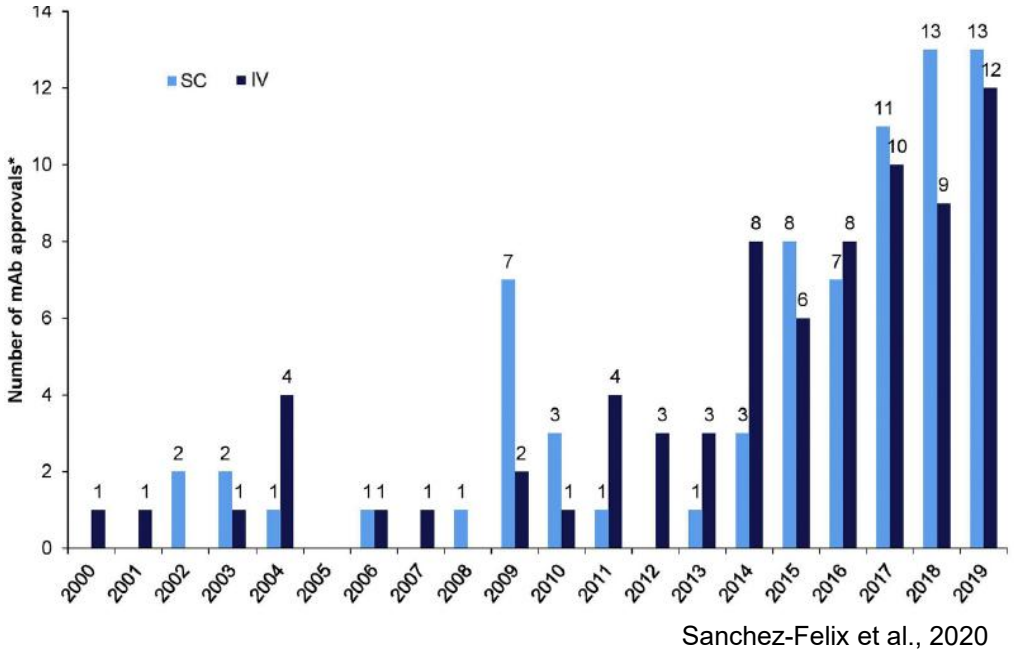
- From IV to SC; how to bridge to the right SC dose regimen (Lymphatics on-chip, Model Informed Drug Development (MIDD))

- From SC to SC; how to bridge from one SC device to the next SC device (*ex vivo* skin injections, µCT imaging)

- From SC to IV; how to bridge to the right IV regimen (MIDD)

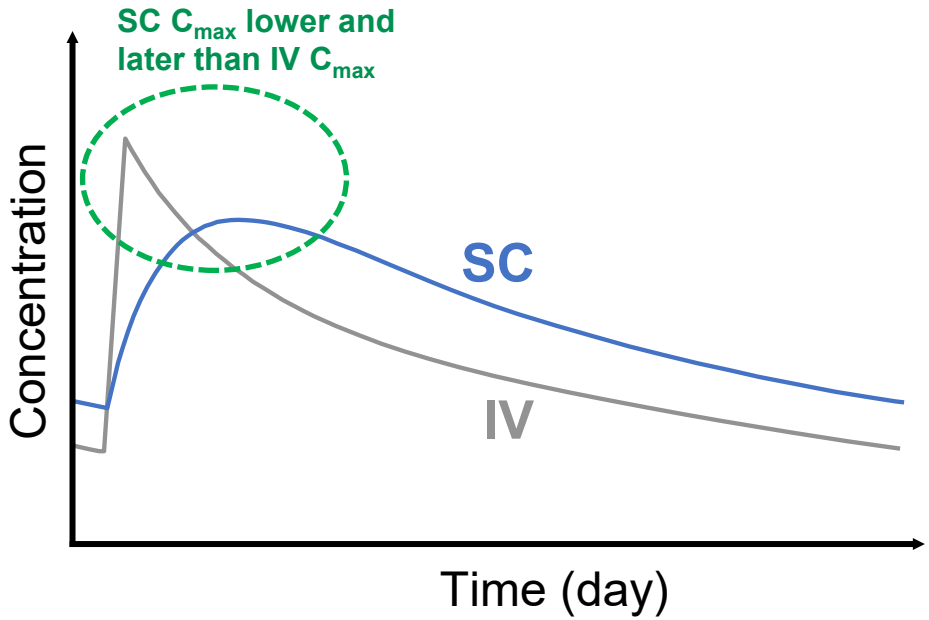
Successful development of SC biotherapeutics requires early bioavailability assessment

Increasing trend towards SC injection of mAbs



Sanchez-Felix et al., 2020

Poor SC bioavailability may compromise feasibility



Poor understanding of mAb SC bioavailability

Costly and lengthy formulation development

Need for predictable preclinical models

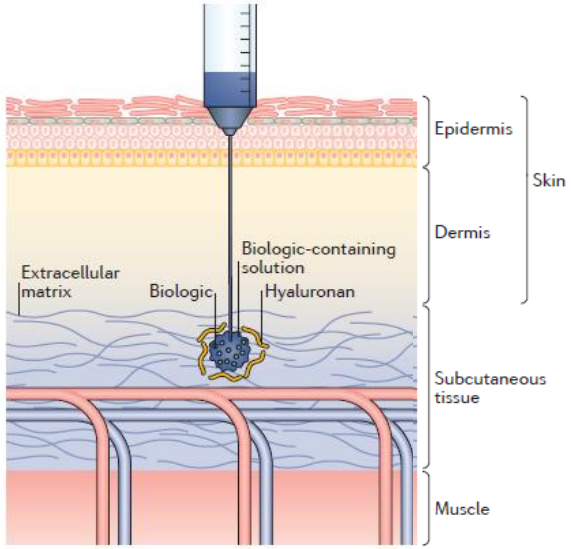
Potential factors influencing SC bioavailability of biotherapeutics

- **Molecular size** (lymphatic vs capillary uptake)
- **Interaction** propensity with **extracellular matrix** (e.g. via charge-charge interactions with collagen, hyaluronic acid...)
- **Aggregation** propensity (e.g. in less favourable pH after diffusion of formulation excipients)
- **Degradation** propensity (e.g. via ROS)
- **Target-mediated disposition during absorption phase**
- **Injection site**
- **Patient body weight**
- **Injection volume, depth, rate, viscosity, molality????**
- ...

IV to SC

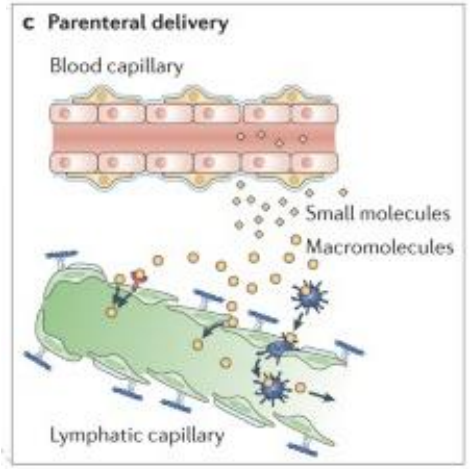
- From IV to SC; how to arrive at the right SC dose regimen

Lymphatic contribution to SC absorption of biotherapeutics



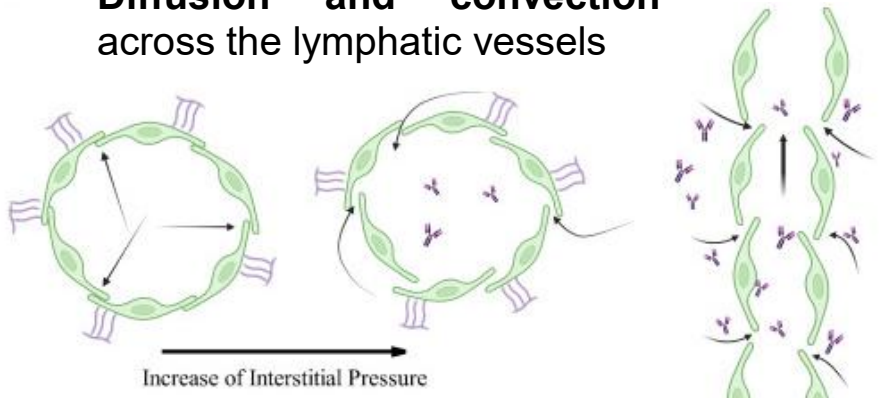
Anselmo et al., 2019

SC lymphatic vasculature is responsible for **SC absorption** of molecules **>16 kDa**



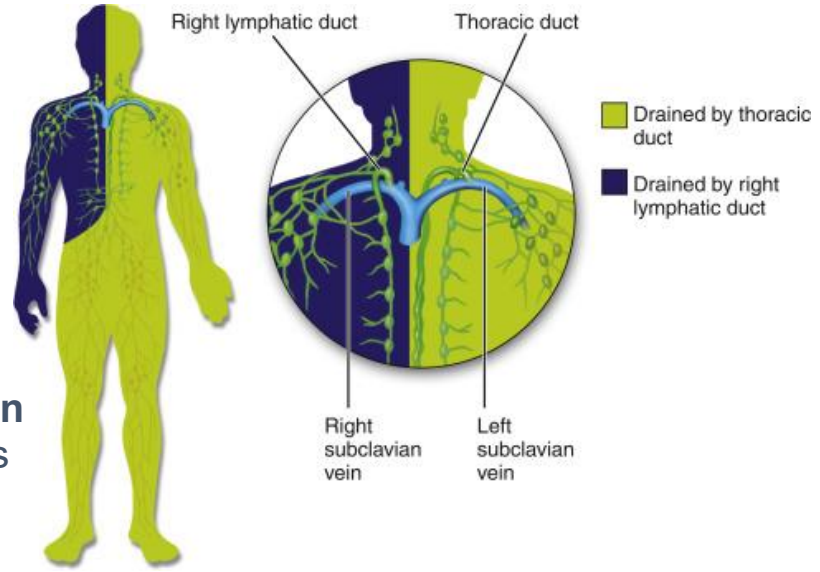
Trevaskis et al., 2015

Diffusion and convection across the lymphatic vessels



Han et al., 2023

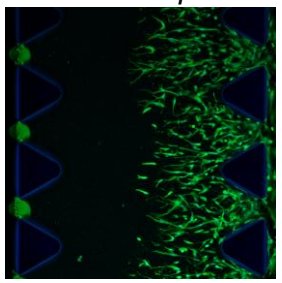
Drainage into systemic circulation via subclavian veins



Lymphatics on-chip: a promising *in vitro* tool to model SC absorption

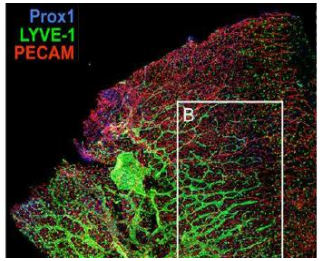
Lymphatics on-chip

On-chip



Lymphatic capillaries

In vivo



Serrano, J. C. et al., 2023

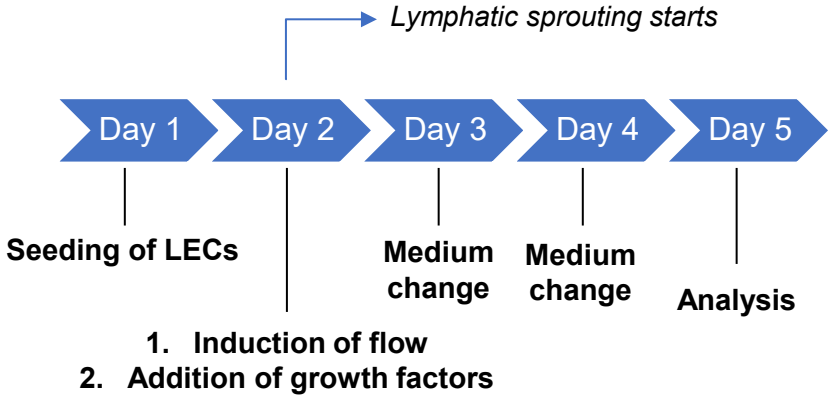
- The lymphatics on-chip models the **subcutaneous interstitium** and **lymphatic vasculature**
- Used to quantify mAb **lymphatic transport** as **key predictor of sc bioavailability**
- Developed in **collaboration with MIT** (Roger Kamm's lab)

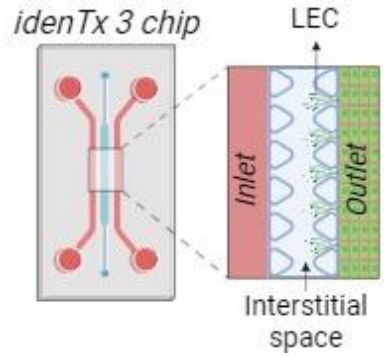
HDD Humanizing Drug Development

Goal: implement the lymphatics on-chip model to assess lymphatic absorption of a panel of internal mAbs and perform IVIVC with clinical SC bioavailability data

Lymphatics on-chip recapitulates the physiology of subdermal lymphatics

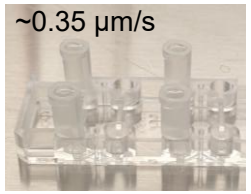
1-week workflow

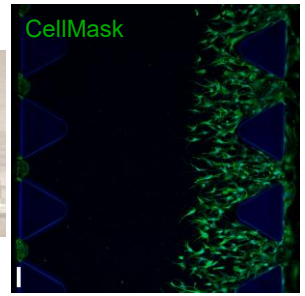




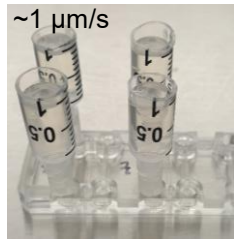
Physiological convective flows and capillary morphology

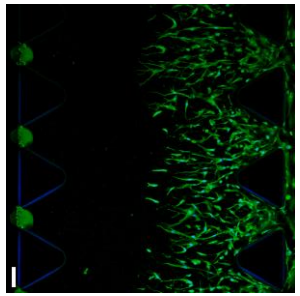
Luer (low flow)





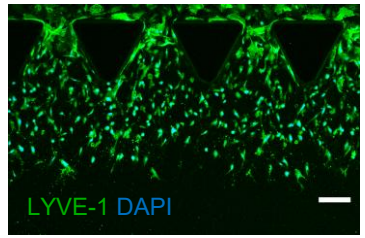
Syringe (high flow)

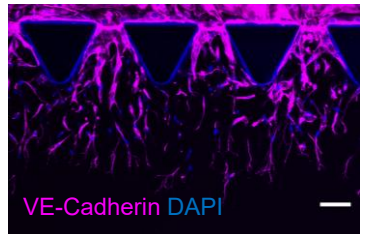




	In Vivo	High flow
Vascular Density (%)	15-30	14.33
Length (µm)*	200-800	~651.10
Diameter (µm)	10-50	~10.09

Phenotypic marker expression

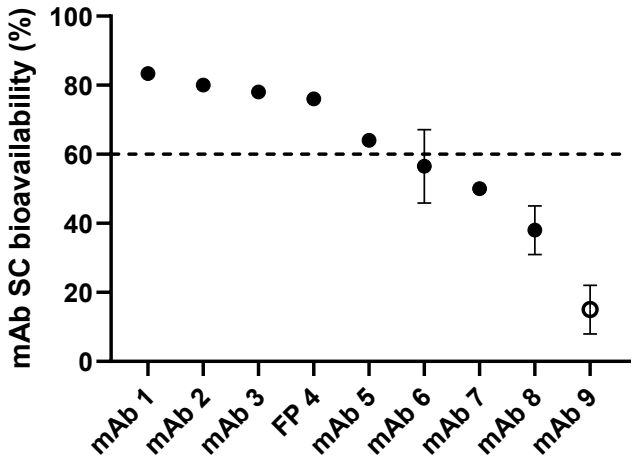




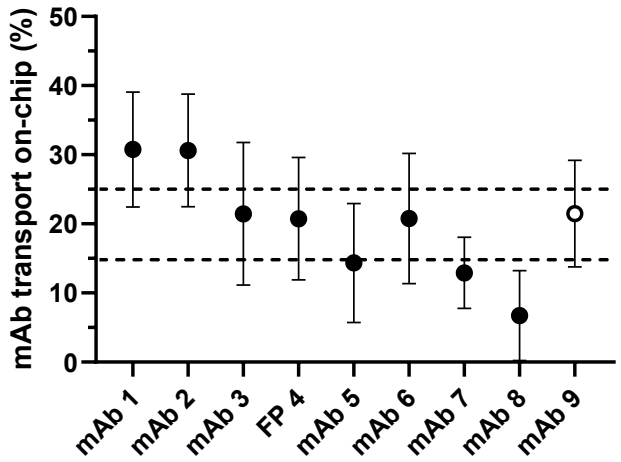
Gabriela Misiewicz

Lymphatics on-chip successfully ranked SC absorption of mAbs

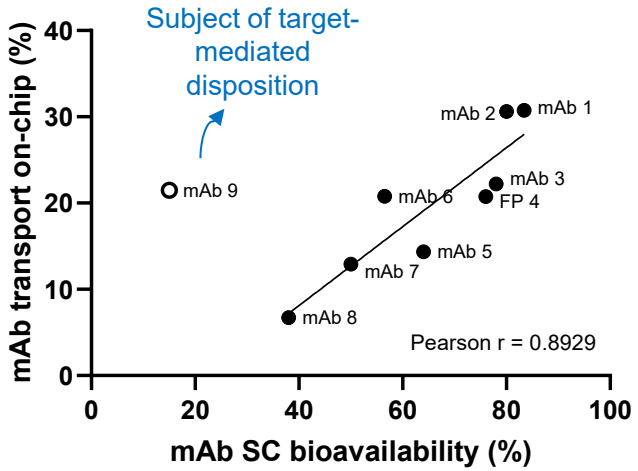
Clinical data



On-chip



IVIVC

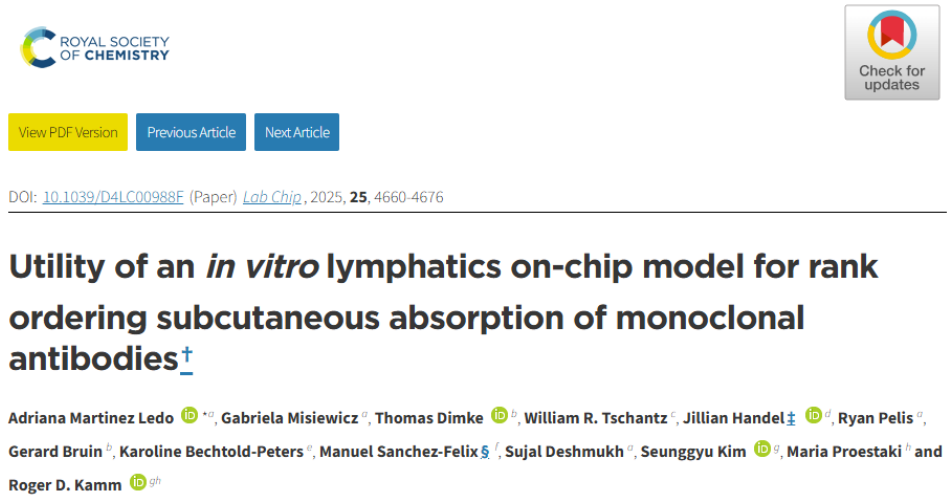


The **good IVIVC** for the 9 therapeutic proteins tested highlights the **potential** of the model for use as a gating tool **for candidate selection in Discovery**

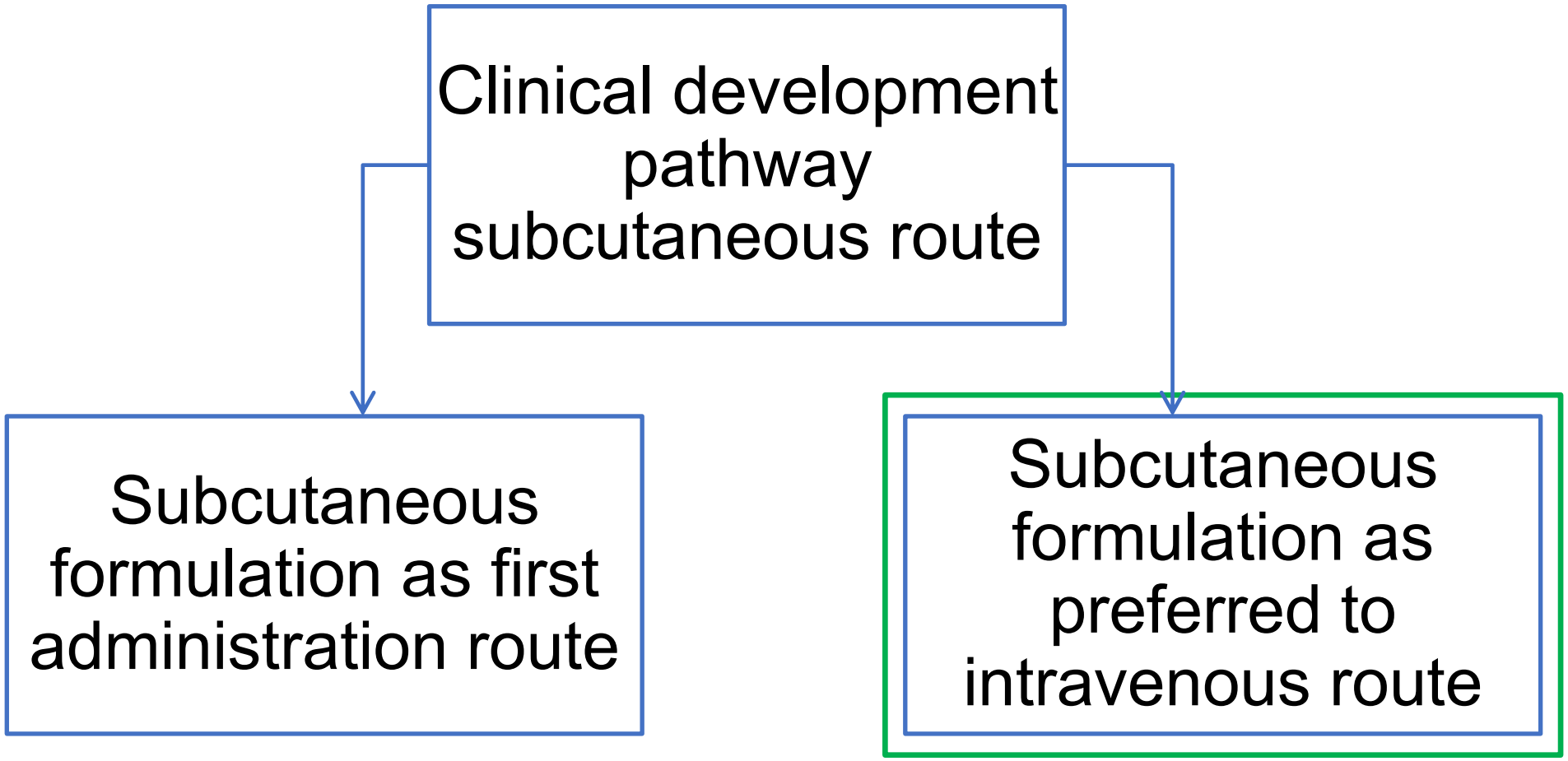
Conclusions, challenges and opportunities for Lymphatics on-chip

- Implementation and evaluation of lymphatics on-chip model resulted in a positive correlation between lymphatic transport and human SC bioavailability
  - Tool for ranking SC absorption during candidate selection/affinity maturation
  - Potential to expand to other biotherapeutics delivered SC

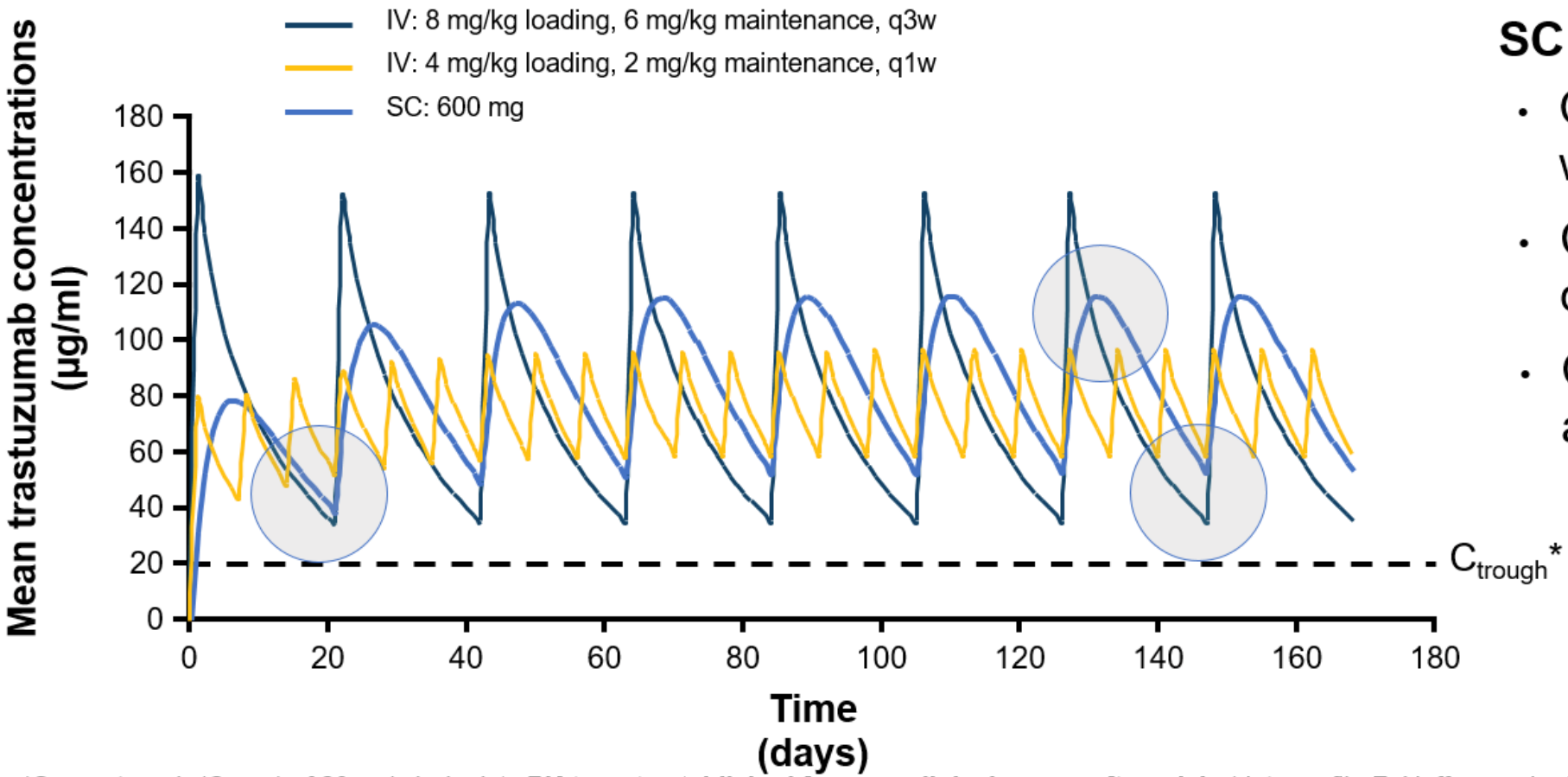
- Model technically challenging
  - Simplify/automate model
  - Position model relative to other available *in vitro* tools



SC administration of mAbs - Development pathway depends on prior availability of IV PK/PD



PK-based clinical bridging approach



SC dose selection concept:

- C_{trough} as least as high as with IV regimen
- C_{max} bracketed by C_{max} of q1w & q3w IV regimens
- Comparable AUC with IV and SC regimens

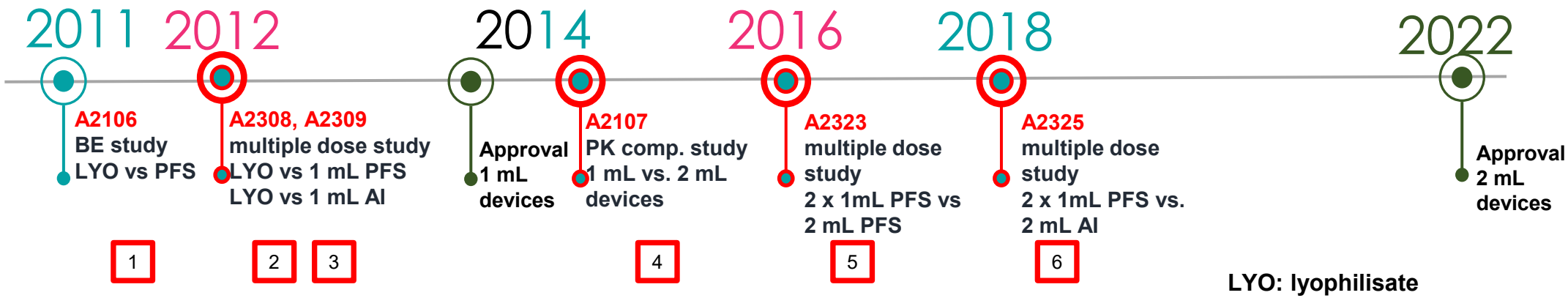
*Serum trough (C_{trough}) of 20 µg/mL depicts **PK target established from preclinical xenograft models** (data on file F. Hoffmann–La Roche; Friess *et al.* Clin Cancer Res 2005.)

SC to SC: how to bridge to the final Drug-Device-Combination-Product (DDCP) in the development program?

Is it really needed to take so much time and studies?

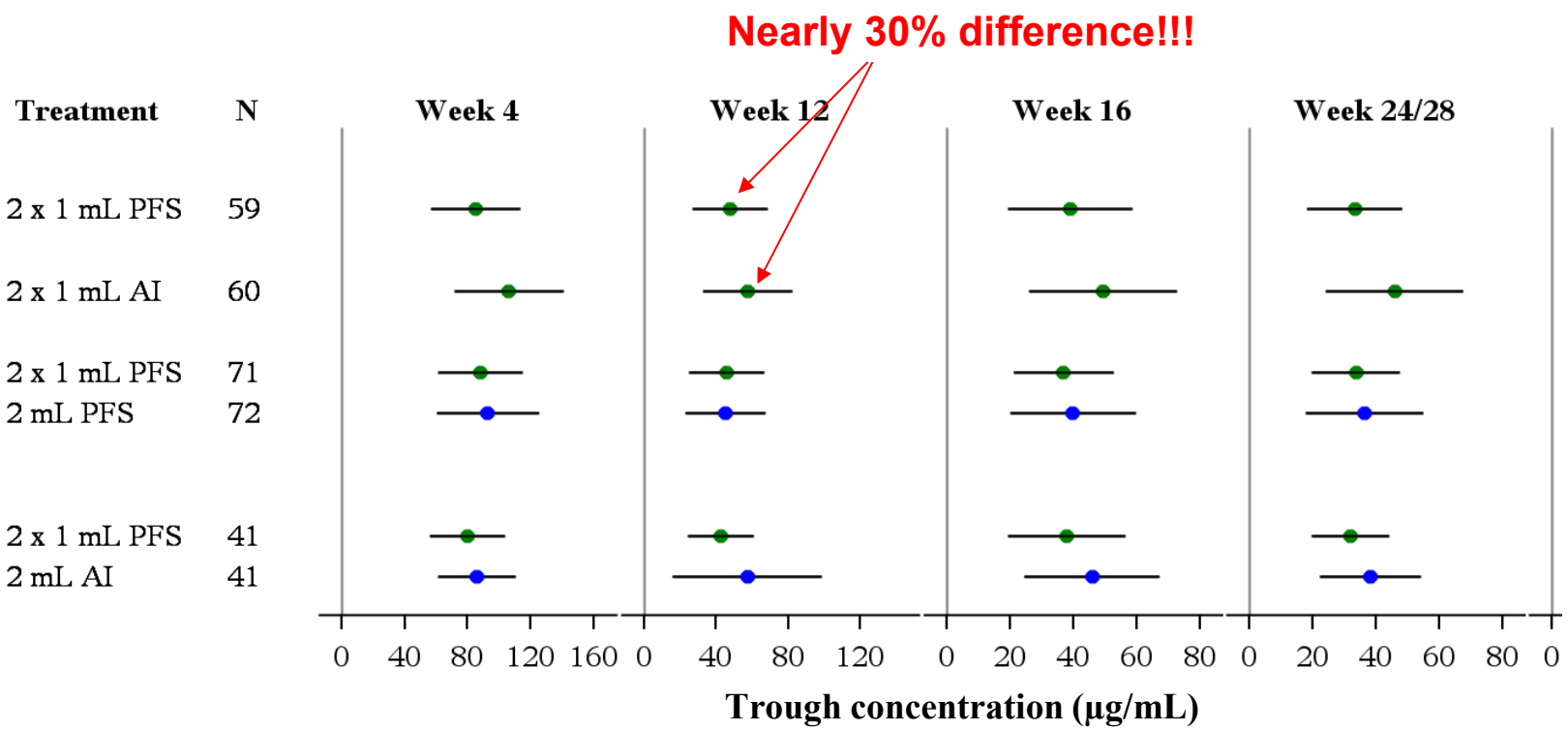
Cosentyx® (secukinumab)

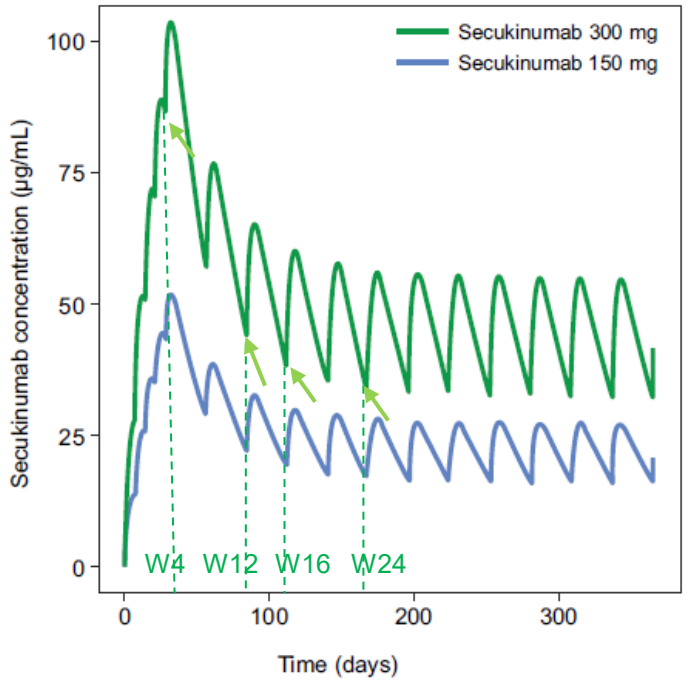
	Drug	From	To	Clinical study	HV/Patients	Number of subjects / arms	HA request	Comment
1	secukinumab	300 mg, 2 x 1 mL LYO,	300 mg, 2 x 1 mL PFS	AIN457A2106 single dose BE	HV	141 / 2	N	with excipients change from LYO to PFS
2		150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 1 or 2 x 1 mL PFS	AIN457A2308 multiple dose Phase 3	Pso	174 / 3	Y	
3		150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 2 x 1 mL AI Delta	AIN457A2309 multiple dose Phase 3	Pso	177 / 3	Y (FDA only)	
4		300 mg, 2 x 1 mL PFS or 2 x 1 mL AI Delta	300 mg, device prototypes	AIN457A2107 single dose – PK comparability	HV	122 / 6	N	Abdomen/thigh, injection time comparison
5		300 mg, 2 x 1 mL PFS	300 mg, 2 mL PFS	AIN457A2323 multiple dose Phase 3	Pso	214 / 3	Y	Abdomen/thigh comparison
6		300 mg, 2 x 1 mL PFS	300 mg, 2 mL AI YpsoMate	AIN457A2325 multiple dose Phase 3	Pso	122 / 3	Y (FDA only)	Abdomen/thigh comparison



LYO: lyophilisate
PFS: prefilled syringe
AI: auto-injector

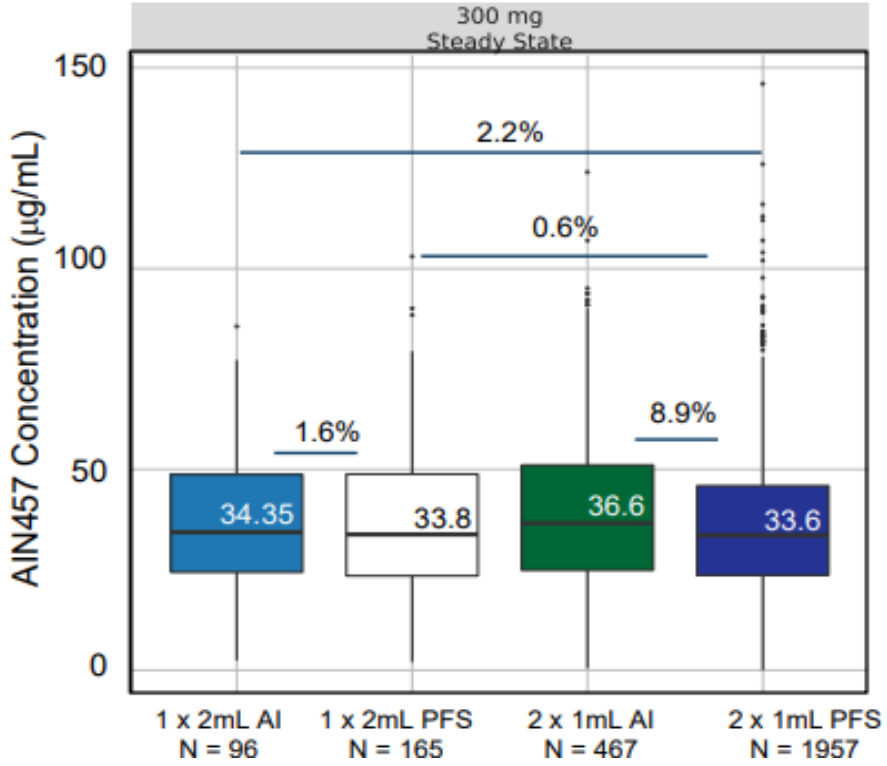
Things can go wrong in cross-study comparisons with sparse PK!





Simulated concentration profiles of secukinumab 300 and 150 mg with subcutaneous dosing regimens derived from phase 3 trials. Patients were simulated to receive secukinumab at baseline; weeks 1, 2, and 3; and then every 4 weeks from week 4 to week 48.

Combined Ph III studies with psoriasis (PsO) and psoriatic arthritis (PsA) patients



Many more patients

Studies	N	2x1mL PFS	2x1mL AI	1x2mL PFS	1x2mL AI
A2308	135	X			
A2309	147		X		
A2323	323	X		X	
A2325	181	X			X
F2312	236	X			
F2318	320		X		
F2342	570	X			
F2366	773	X			

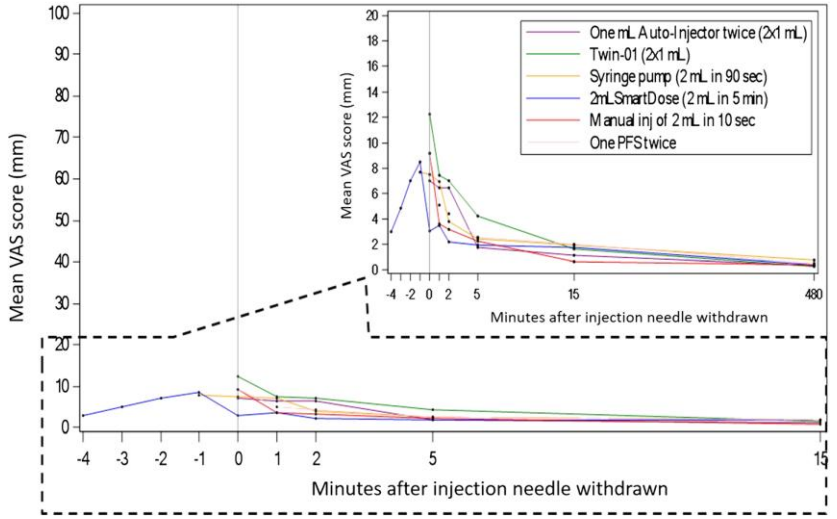
4 PsO Phase 3 studies

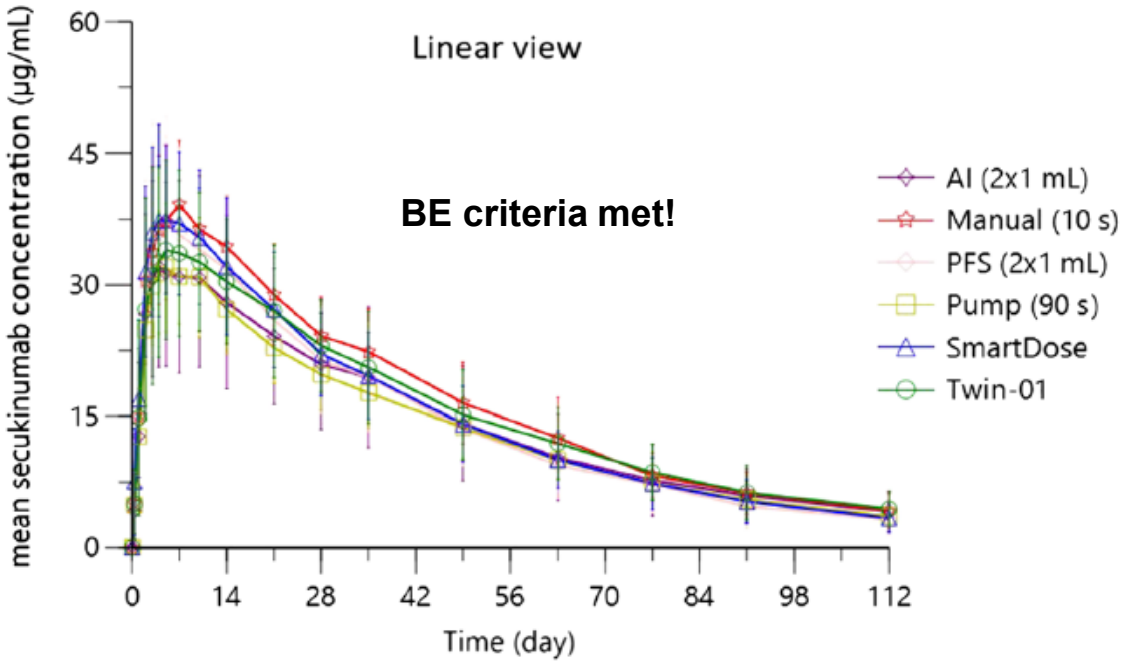
4 PsA Phase 3 studies

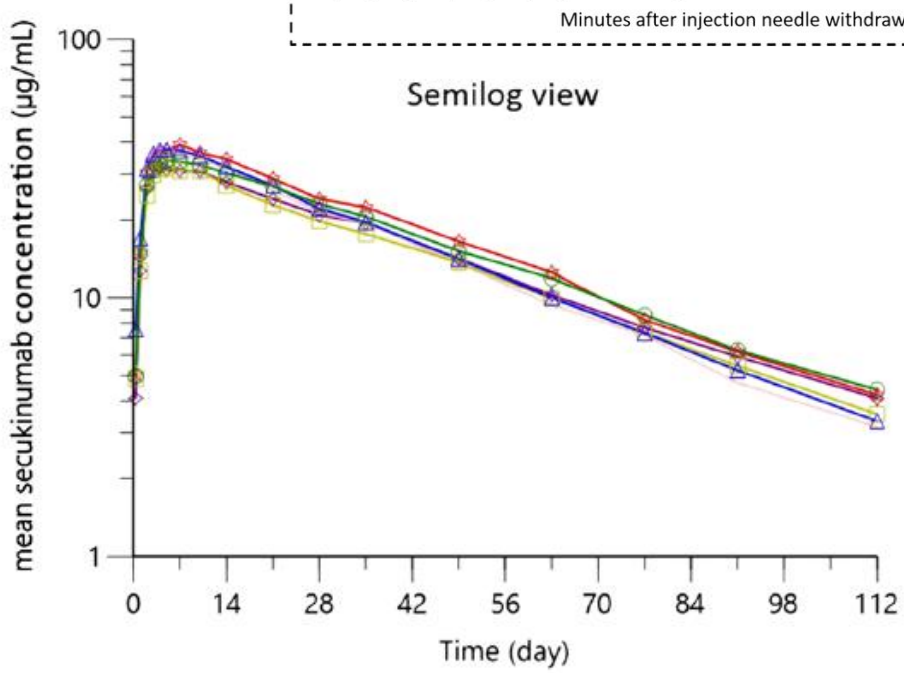
No impact of DDCP on PK, clinical efficacy, and safety!

Comparable PK with 2 mL injection volumes and injection times between 10 seconds and 5 minutes

	Needle length/estimated depth of injection	Injection time	Short label [a]
Auto-injector twice, 2 × 1 mL	12 mm/8 mm	10 s	AI (2 × 1 mL)
Twin-01, 2 × 1 mL	12 mm/8 mm	10 s	Twin-01
Syringe pump, 2 mL in 90 s)	6 mm	90 s	Pump (90 s)
2-mL SmartDose, 2 mL in 5 min	5 mm	5 min	SmartDose
Manual injection, 2 mL in 10 s	12 mm/8 mm	10 s	Manual (10 s)
One PFS twice, 2 × 1 mL	12 mm/8 mm	10 s	PFS (2 × 1 mL)
One 2-mL PFS, 2 mL	12 mm/8 mm	10 s	PFS (2 mL)



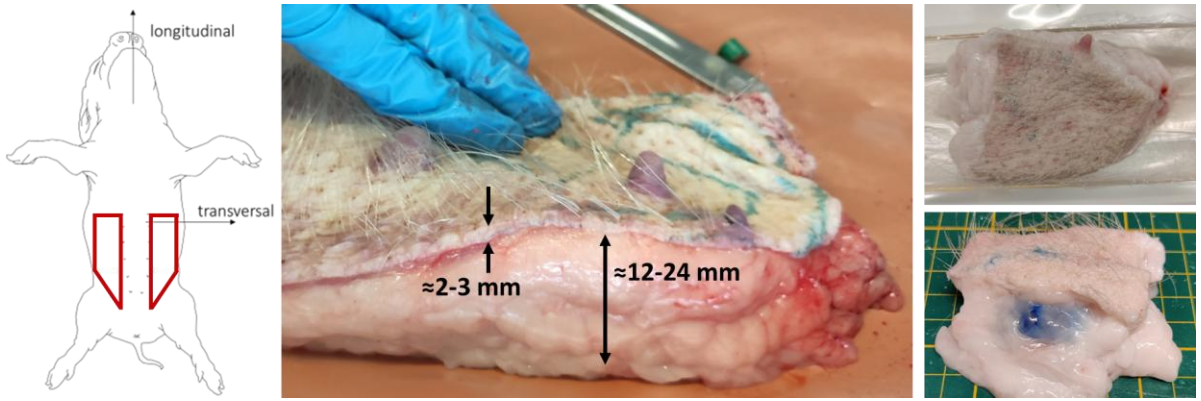




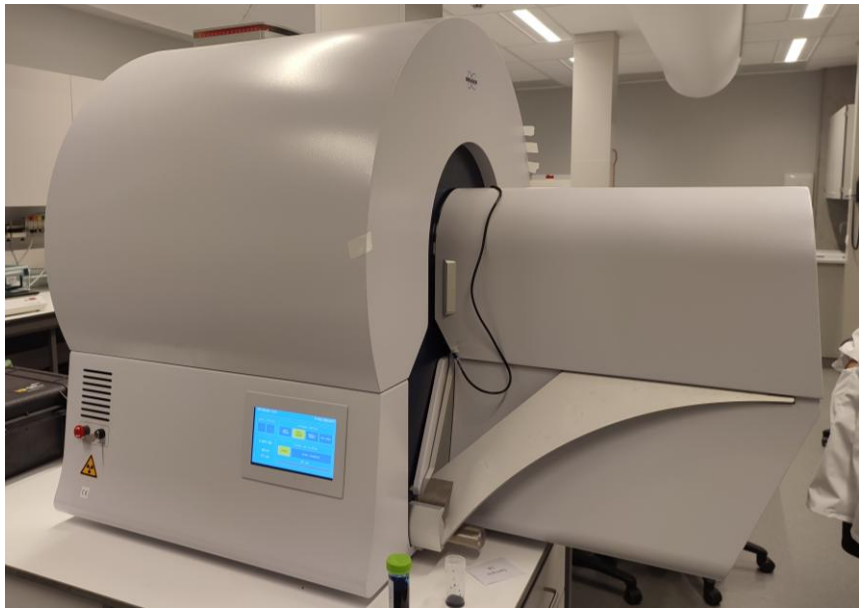
Ex vivo evaluation of dispersion of liquid volume plugs after SC bolus administration

- CRUX/Novartis started to investigate dispersion of liquid volumes in an *ex vivo* minipig and human model by using µ-computed tomography (µ-CT) (see next slide).
- Nonclinical *ex vivo* studies are convenient for tissue acquisition and handling, and the ability to scan smaller samples at much higher resolution in a µ-CT setup.
- Visualization of the 3D pattern and location of SC fluid dispersion in minipig abdominal tissues immediately after injection.
- Results so far can be regarded as a first step towards establishing a generalized baseline for small (≤2 mL) and large injection volumes (5 mL) of aqueous formulations.

SC Injections of Different Volumes, Viscosities and Injection Rates: an *ex vivo* minipig micro-CT Study



Left: diagram showing anatomical region of samples. Centre: tissue flap from minipig abdomen, with typical skin and fat thickness dimensions. Right: sample before (top) and after (bottom) injection.



micro-CT scanner with injection tubing

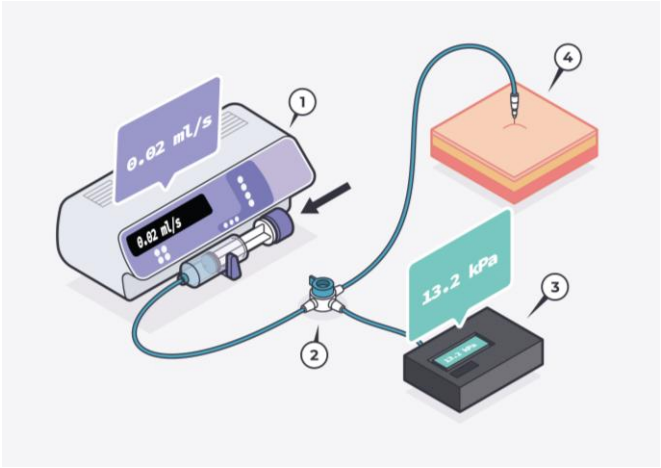
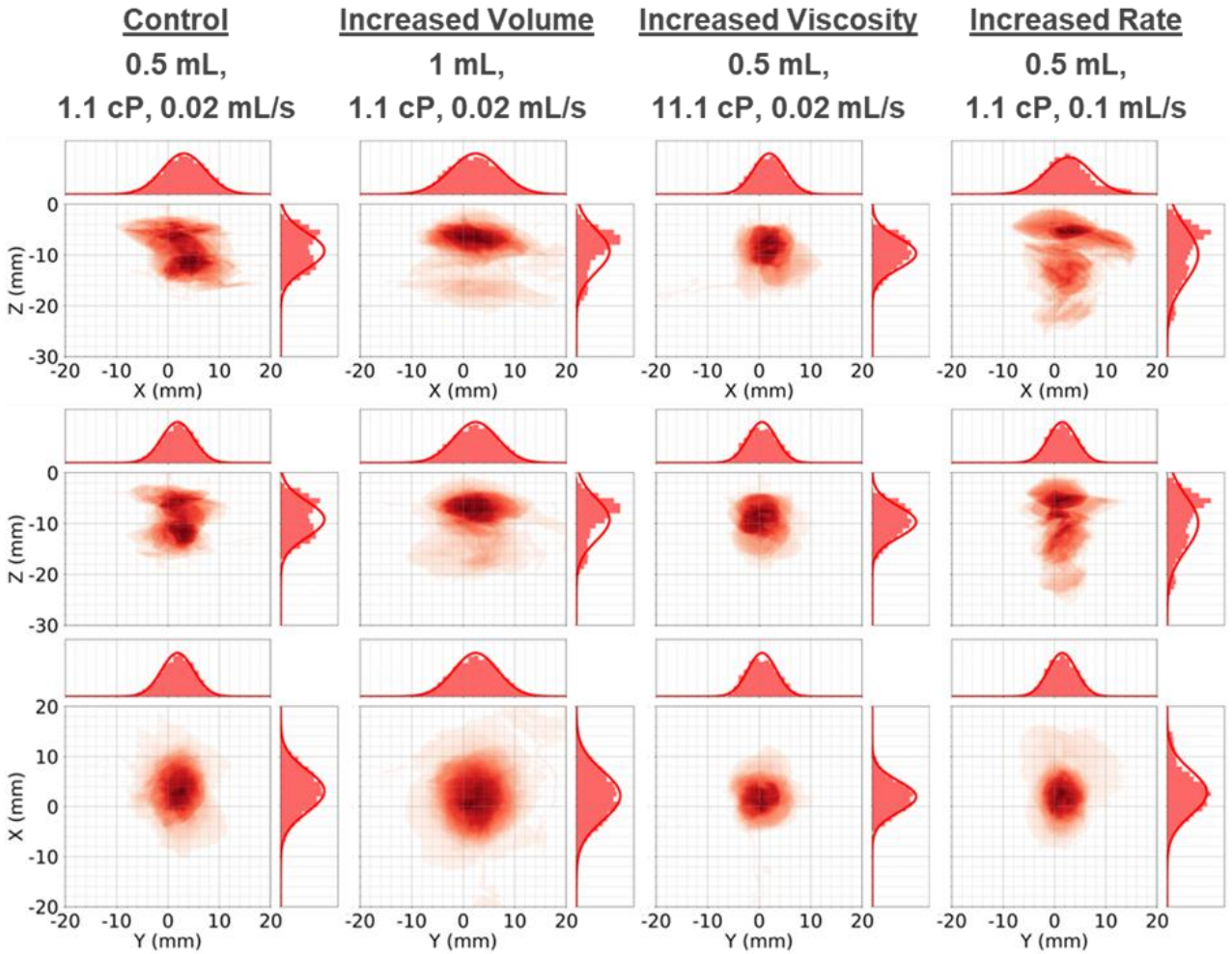
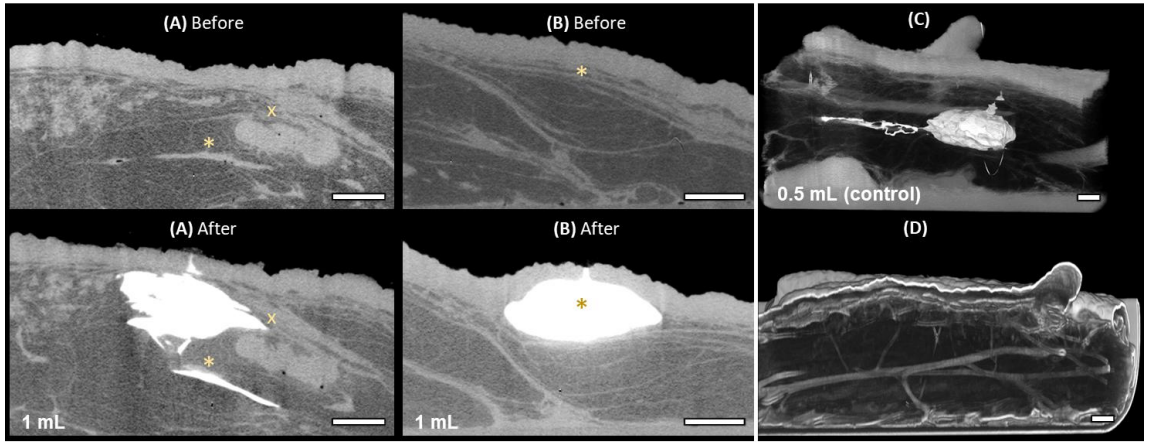


Diagram of setup with (1) Syringe pump, (2) Stopcock, (3) Pressure logger, (4) Tissue sample.

Test group	Viscosity [cp]	Rate [mL/s]	Volume [mL]	Repeats
1) Control	1.1	0.02	0.5	5
2) Increased volume	1.1	0.02	1.0	5
3) Increased viscosity	11.1	0.02	0.5	5
4) Increased rate	1.1	0.1	0.5	5

Overlaid orthogonal views and histograms





(A, B) micro-CT images showing sample slices at the needle insertion location before and after injection, with markers (*, x) to indicate corresponding regions of interest. (C) 3D render of 0.5 mL bolus in tissue sample, placed below a dense region of tissue (possibly fascia), with a channel of fluid extending far to the left of the bolus, indicating that the fluid has entered a blood or lymph vessel. (D) 3D render of vasculature for one sample pre-injection, showing the distribution of blood and/or lymph vessels under the skin. Scalebar 5 mm.

Journal of Pharmaceutical Sciences 113 (2024) 3447–3456
Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org
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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Visualisation and quantification of subcutaneous injections of different volumes, viscosities and injection rates: An *ex-vivo* micro-CT study

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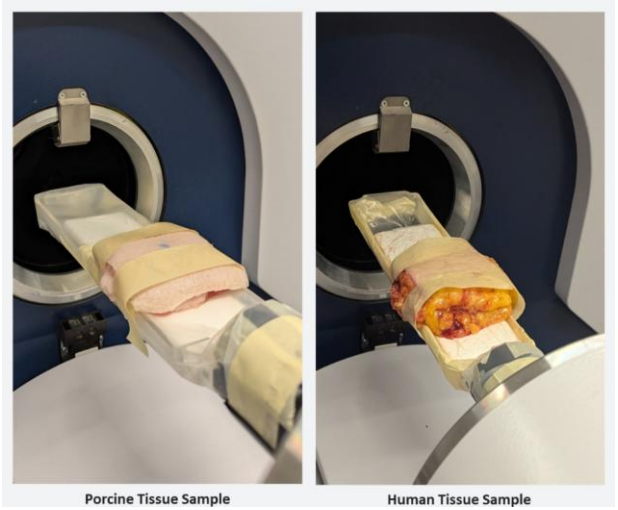
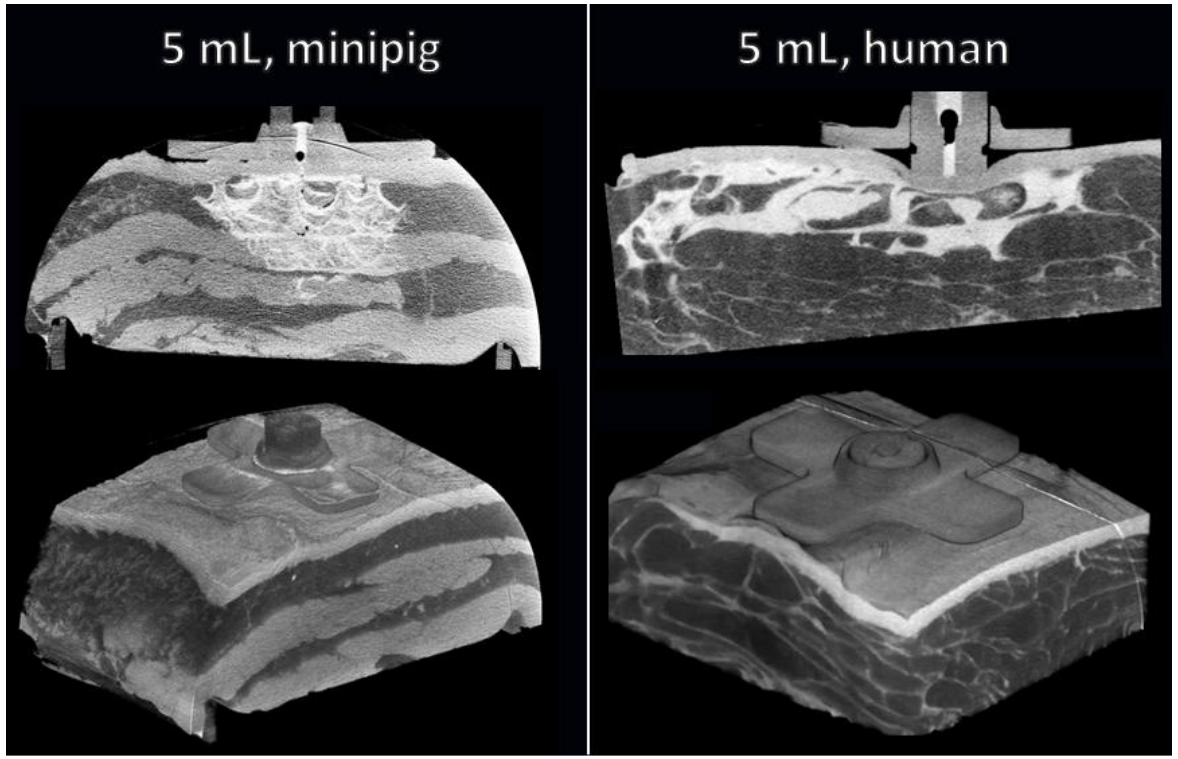
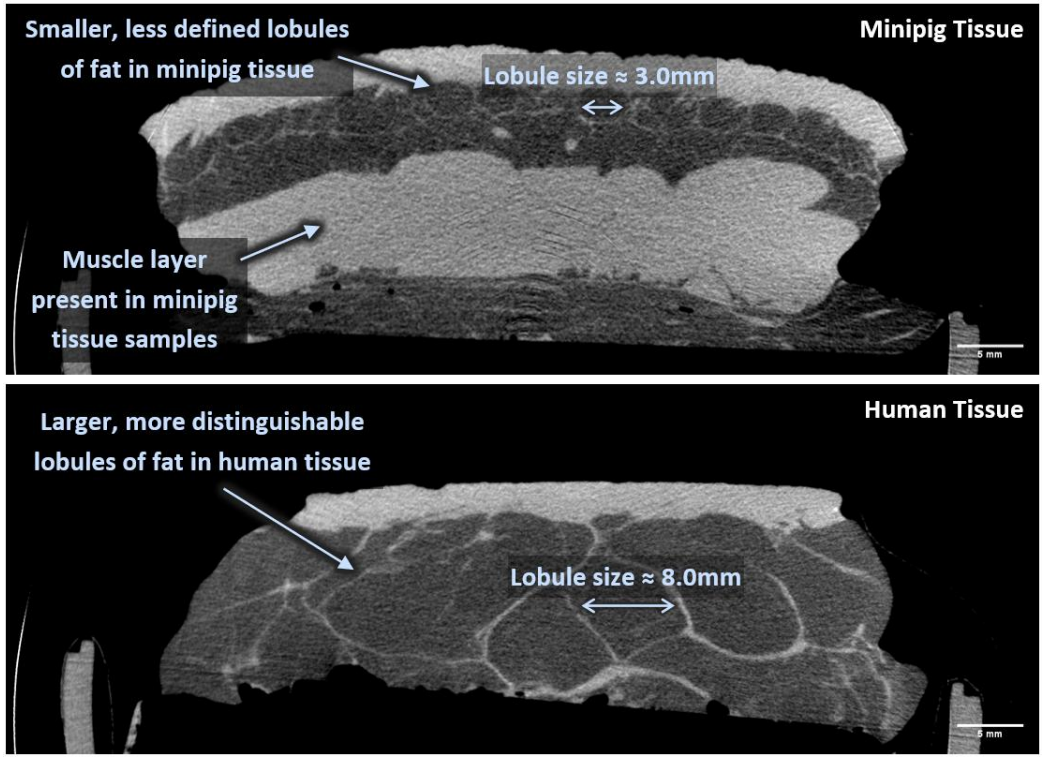
Porcine-Human Translatability

***Ex vivo* study suggest differences in tissue structure to strongly influence drug dispersion:**

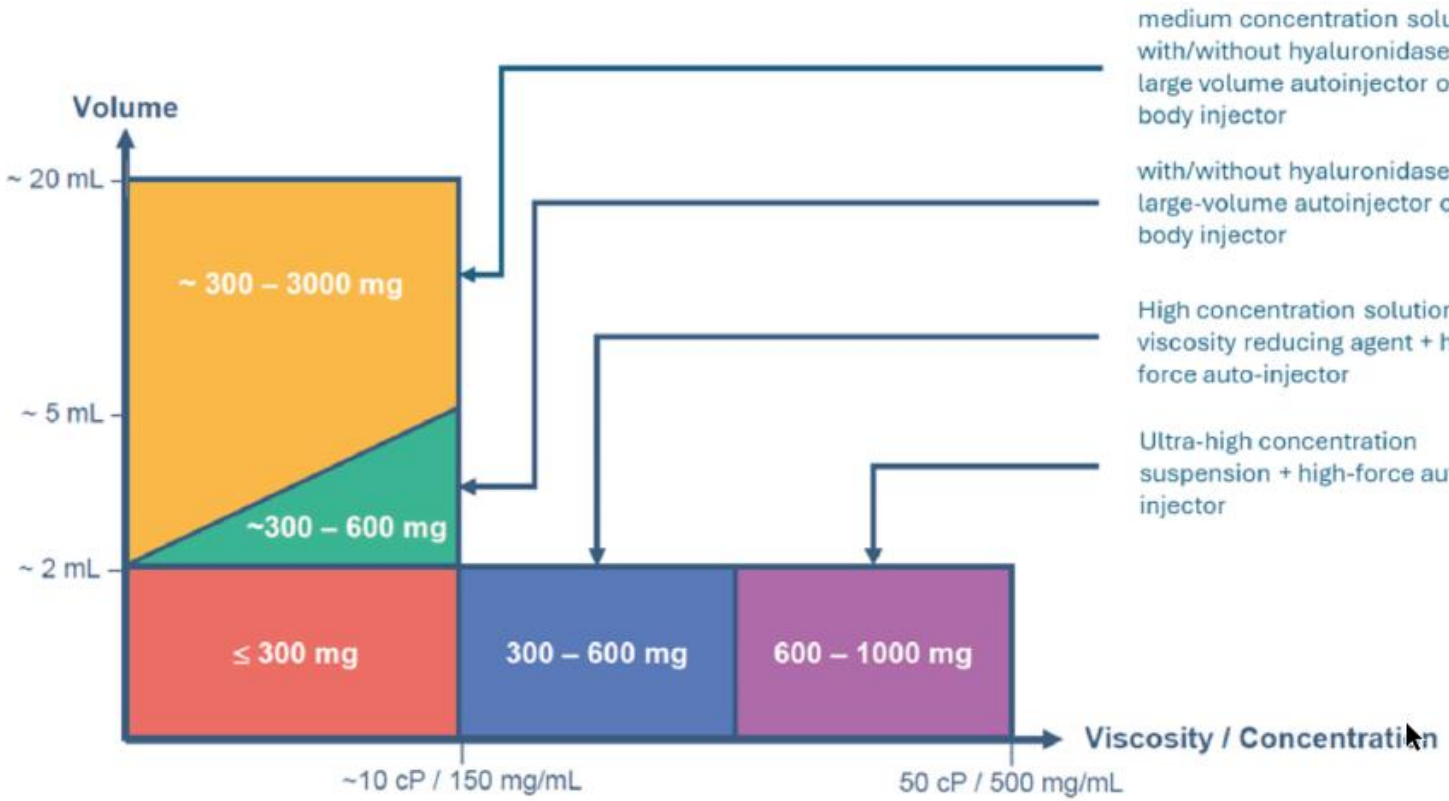
- Tissue layer thickness
- Lobule size and shape
- Mechanical stiffness and strength
- Investigate effect of volume (1 mL *vs.* 5 mL) and viscosity (1 *vs.* 10 *vs.* 50 cP)







Options to achieve doses >300 mg and accompanying impact on viscosity, formulation and device



Journal of Controlled Release 386 (2025) 114156

Contents lists available at ScienceDirect

Journal of Controlled Release

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An industry perspective on clinical development and regulatory strategies for subcutaneously administered high-dose biologics

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[c] Sanofi, 100 Morris Street, Morristown, NJ 07960, USA
[d] GSK, 1250 South Collegeville Road, Collegeville, PA 19426, USA
[e] J&J Innovative Medicine, 335 Phoenixville Pike, Malvern, PA 19355, USA
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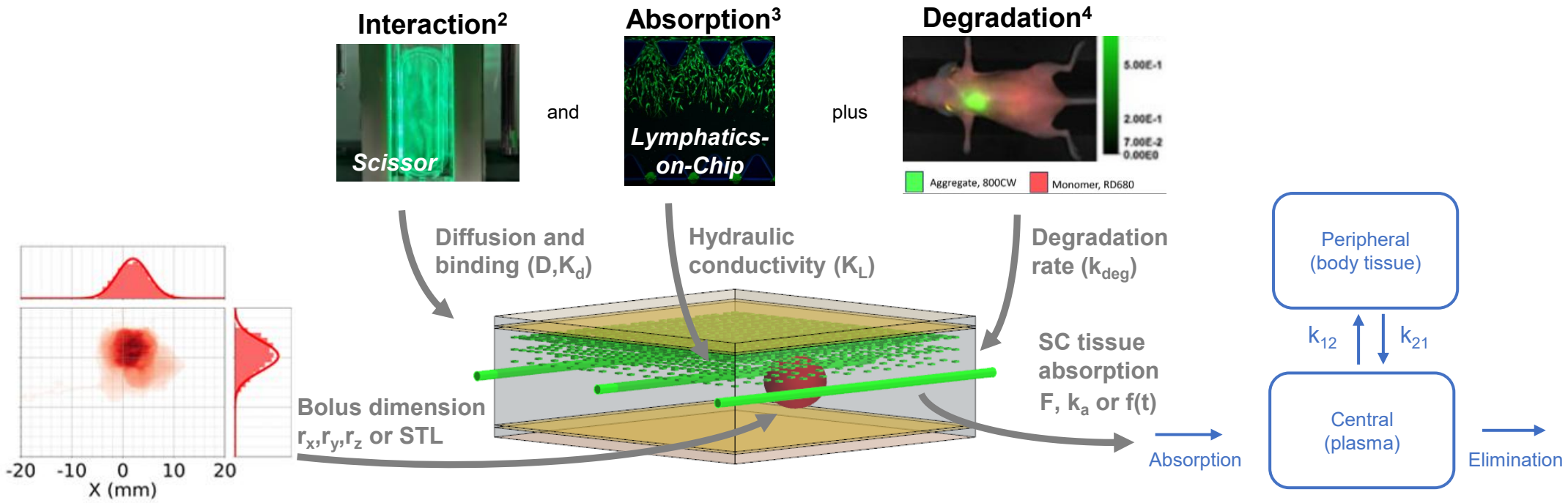
[g] Novartis, WSJ-158, CH-4002 Basel, Switzerland
[h] Merck & Co., Inc., 126 E. Lincoln Ave., Rahway, NJ 07065, USA
[i] BD Technologies and Innovation, 21 Davis Dr, Durham, NC 27709, USA
[j] BD Pharmaceutical Systems, 1 Becton Drive, Franklin Lakes, NJ 07417, USA
[k] J&J Innovative Medicine, 510 Cottonwood Dr, Milpitas, CA 95035, USA
[l] F. Hoffmann-La Roche, Grenzacher Str. 124, CH-4070 Basel, Switzerland

When everything comes together



Bolus Imaging[1]

local distribution informed by ex vivo experiments

Absorption Model

local absorption informed by in vitro/degradation exp.

Compartment Model

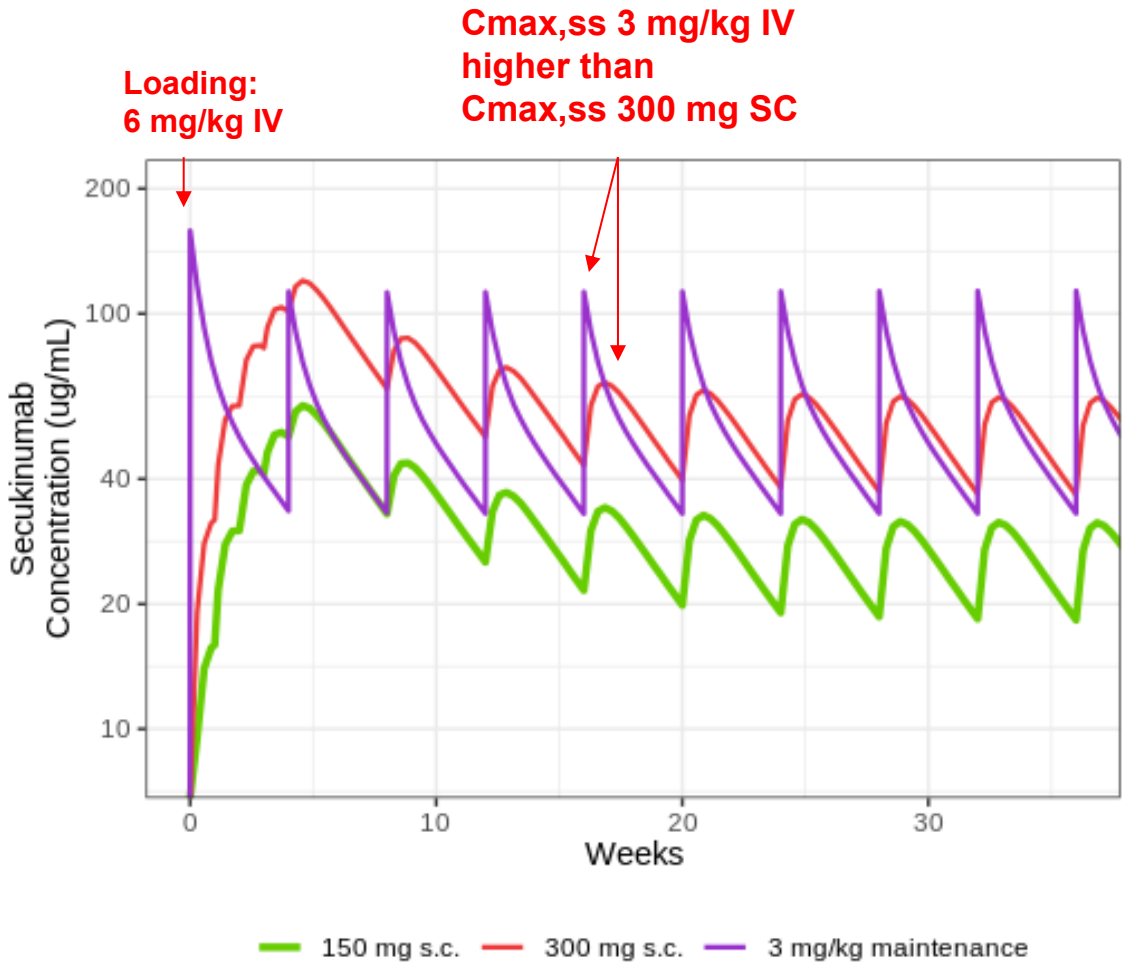
systemic disposition informed by IV study

1) Data from collaboration published together with Crux
2) Internal data (not published yet)
3) Internal data (published)
4) Image from Leiden publication (Filipe 2014)

From SC to IV: how to bridge to the right IV regimen?

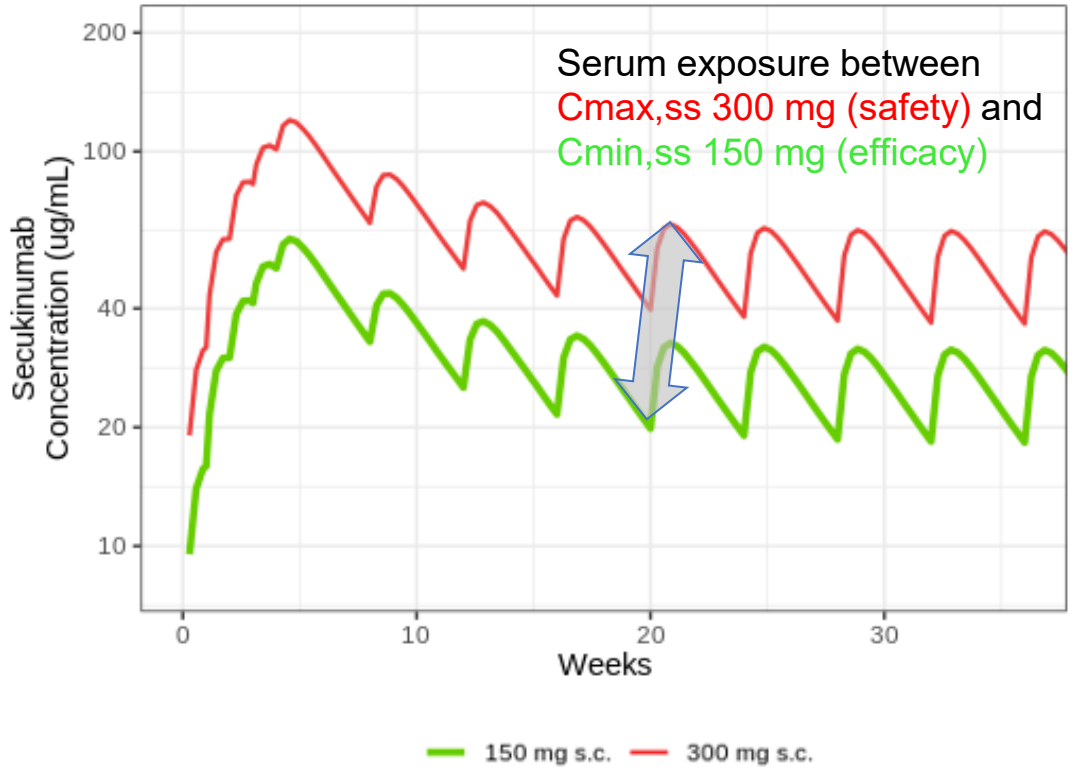
Brief development history (2019)

- Cosentyx was approved for doses of 150 mg SC and 300 mg SC in Spondyloarthritis (SpA) (2015)
- Two Phase III studies were conducted to test a new IV regimen (6 mg/kg IV loading, then 3 mg/kg IV, q4w) in SpA
- This regimen was discussed (and we thought agreed!) with FDA
- 2021: The IV studies were positive and confirmed the expected efficacy and safety profile like SC
- But FDA's Pre-BLA feedback:
  "... IV regimen appears to result in higher Cmax ..." and "We are concerned that your IV regimen may not have sufficient information to support the benefit-risk assessment ..., particularly for more rare and latent AEs"
- FDA also hinted at a potential next step using MIDD (Model-Informed Drug Development)

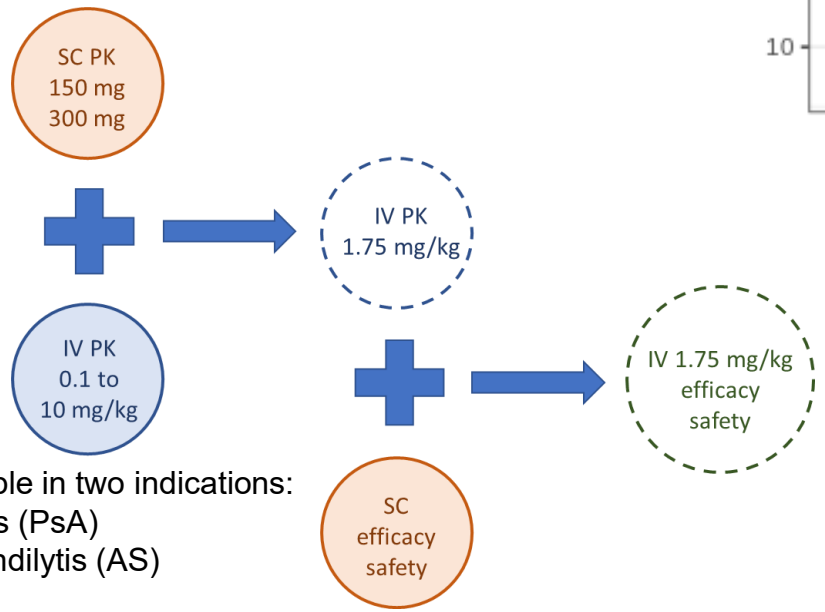


2022 - How can MIDD help?

1. <u>Identification</u> of a new, lower IV regimen that approximates the exposure of the SC regimens
2. Extrapolation of the efficacy and safety from the SC regimens to a lower IV regimen based on: Same exposure with IV and SC will lead to same efficacy/safety

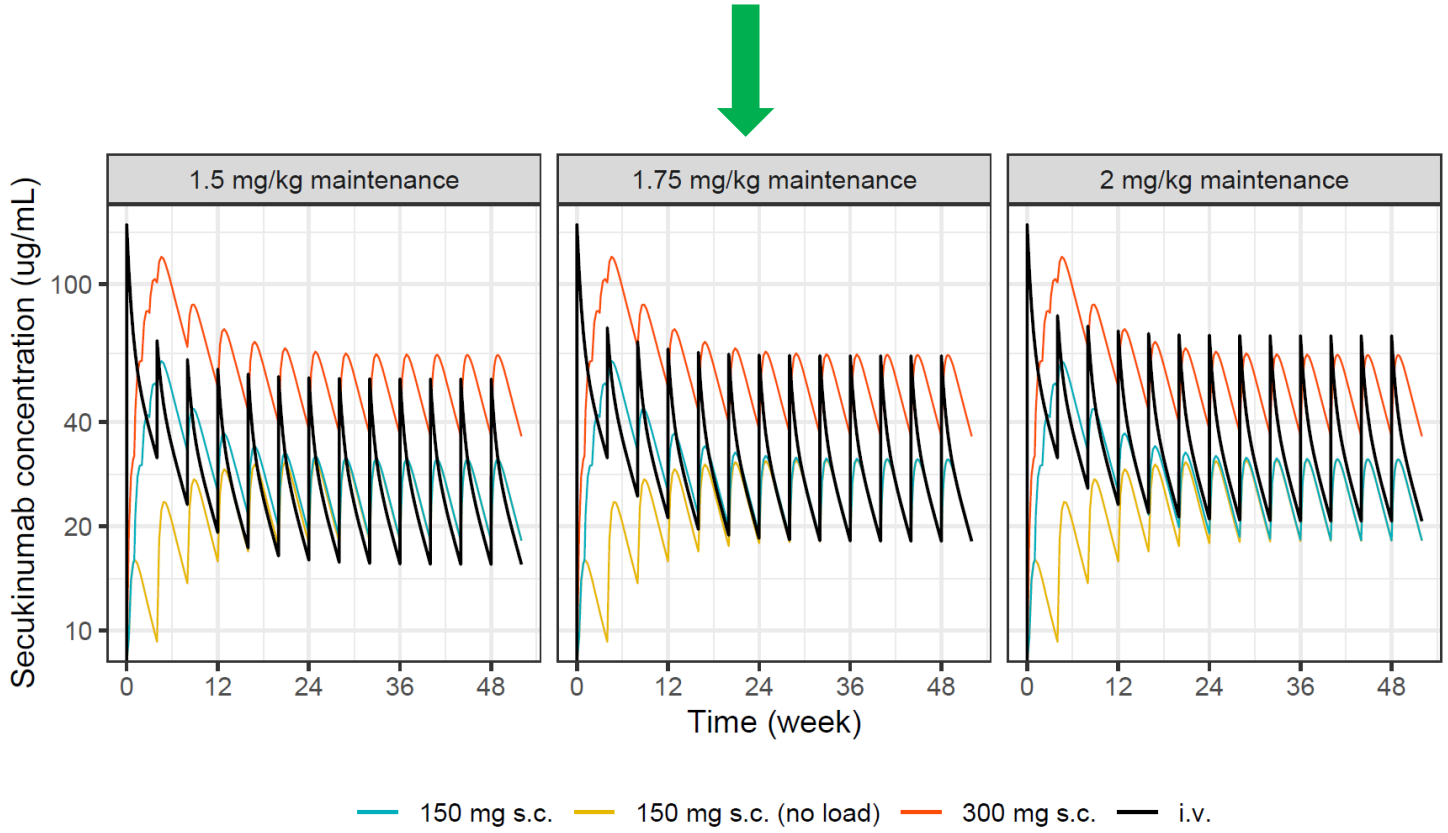


SC PK data available in three indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)
- nonradiographic-axial Spondyloarthritis (nr-axSpA)



IV PK data available in two indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)

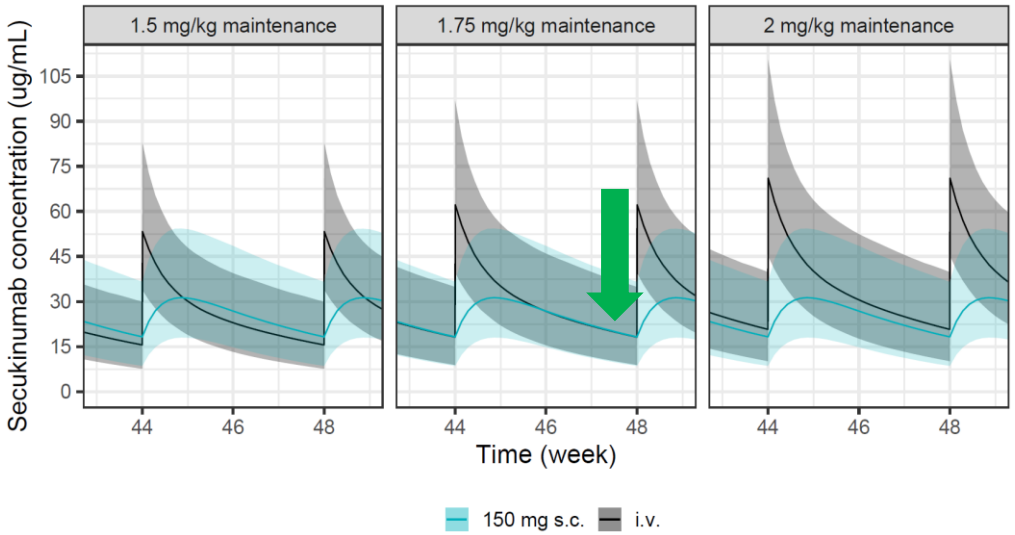
Median predicted PK profiles of three IV regimens that approximate the 150 mg and the 300 mg SC regimens

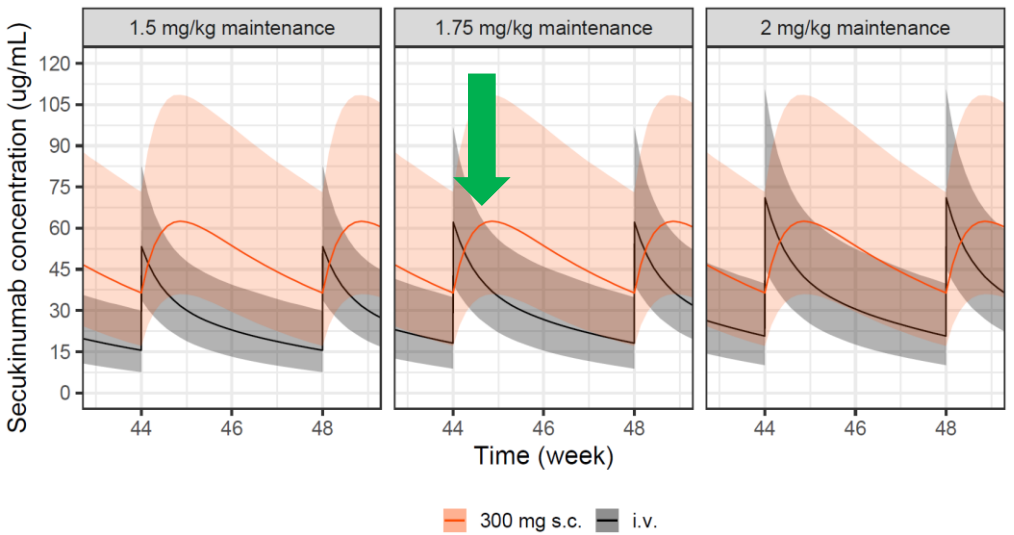


The three IV regimens comprise a 6 mg/kg loading dose at Week 0 followed by a maintenance with 1.5, 1.75, or 2 mg/kg administered q4w starting on Week 4.

The lines represent the median of the secukinumab concentration-time profiles predicted for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, as obtained from the final popPK model.

Distribution of PK profiles at steady-state for three IV regimens and the 150 and 300 mg SC q4w regimen





The lines represent the median of the secukinumab concentration-time profiles simulated for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, obtained from the final popPK model. The ribbons correspond to the 90% PI.

Maintenance regimen	Median (90% PI)		
	Cmin,ss (µg/mL)	Cavg,ss (µg/mL)	Cmax,ss (µg/mL)
1.5 mg/kg i.v. q4w	15.6 (7.6, 29.9)	25.1 (13.7, 45.7)	53.3 (34.0, 83.0)
1.75 mg/kg i.v. q4w	**18.1 (8.9, 34.8)**	**29.2 (16, 53.4)**	**62.1 (39.6, 96.9)**
2 mg/kg i.v. q4w	20.7 (10.2, 39.7)	33.4 (18.2, 61.0)	71.0 (45.3, 110.7)
150 mg s.c. q4w	18.2 (8.6, 36.5)	25.1 (12.3, 50.6)	31.3 (18.0, 54.3)
300 mg s.c. q4w	36.4 (17.2, 73.2)	50.1 (24.6, 101.2)	62.6 (36.1, 108.7)

Dumortier, T., Valenzuela, G., Churchill, M., Mijatovic, J., Bruin, G., Pricop, L., Richards, H., Renard, D., Singhal, A. and Marathe, A. (2025), Model-Informed Drug Development-Based Bridging from Subcutaneous to Intravenous Secukinumab Dosing: Approval in Psoriatic Arthritis and Axial Spondyloarthritis. Clin Pharmacol Ther, 118: 480-488. https://doi.org/10.1002/cpt.3716

Pisal, D.S., Li, Y., Golding, A., Nair, R., Nikolov, N.P., Madabushi, R., Zhu, H., Doddapaneni, S., Sahajwalla, C., Bi, Y. and Chen, J. (2025), Model-Informed Drug Development-Based Approval of Intravenous Secukinumab for the Treatment of Adult Patients with Active Psoriatic Arthritis, Active Ankylosing Spondylitis, and Active Non-Radiographic Axial Spondyloarthritis. Clin Pharmacol Ther, 117: 475-484. https://doi.org/10.1002/cpt.3464

Conclusions

- Significant progress has been made in the
  - development of predictive *in vitro* models for SC bioavailability
  - development of enabling formulation and device technologies
  - understanding of potential impact of dispersion after SC administration on PK
  - in streamlining clinical trial designs

- Key remaining opportunities include advancing and further validating these models

- Bioavailability predictions remain complex, yet continued research has led and will further lead to improved understanding and control. (species differences, tissue interaction, degradation after injection). Stepwise approach needed.

- From a clinical development perspective, PK-based bridging strategies, using MIDD, are becoming standard and can mostly be applied across different indications